APPENDIX B

1. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

2. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said antagonist is in the form of multiparticulates individually coated with a sequestering material which substantially prevents release of the antagonist.

3. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said antagonist is dispersed in a matrix comprising a sequestering material which substantially prevents the release of the antagonist.

4. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist contained in said intact dosage form to the amount of said antagonist released from said intact dosage form after 1 hour is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

5. An oral dosage form comprising (i) an opioid agonist in a releasable form; and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the amount of antagonist released from said intact dosage form after 1 hour is less than an amount bioequivalent to 0.25 mg naltrexone and the amount of said antagonist released after 1 hour from said dosage form after tampering is an amount bioequivalent to 0.25 mg naltrexone or more, said release based on the dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

6. An oral dosage form comprising (i) an opioid agonist in a releasable form; and (ii) sequestered naltrexone or a pharmaceutically acceptable sat thereof which is substantially not released when the dosage form is administered intact, such that the amount of naltexone released from said intact dosage form after 1 hour is less than 0.25 mg and the amount of said naltrexone released after 1 hour from said dosage form after tampering is 0.25 mg or more, said release based on the dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, wherein said agonist and naltrexone are interdispersed and are not isolated from each other in two distinct layers.

7. An oral dosage form comprising (i) a therapeutic effect of an opioid agonist; and (ii) a sequestered opioid antagonist, such that at 1 hour after oral administration, said

dosage form releases not more than 25% of said antagonist, said dosage form providing analgesia and said released antagonist not affecting analgesic efficacy, wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

8. An oral dosage form comprising: (i) an opioid agonist in a releasable form; and an (ii) opioid antagonist in substantially non-releasable form wherein said antagonist is in the form of multiparticulates individually coated with a material that substantially prevents release of the antagonist.

9. An oral dosage form comprising: (i) an opioid agonist in a releasable form; and an (ii) opioid antagonist in substantially non-releasable form wherein said antagonist is dispersed in a matrix comprising a material that substantially prevents the release of the antagonist.

10. The oral dosage form of claim 1 wherein said ratio is 10:1 or greater.

11. The oral dosage form of claim 1 wherein said ratio is 50:1 or greater.

12. The oral dosage form of claim 1 wherein said ratio is 100:1 or greater.

13. The oral dosage form of claim 6 wherein said intact dosage form releases at least 0.025 mg naltrexone at 1 hour.

14. The oral dosage form of claim 1 wherein said intact dosage form provides at least an amount of antagonist bioequivalent to 0.025 mg naltrexone at 1 hour.

15. The oral dosage form of claim 5 wherein the amount of antagonist released after 1 hour from said tampered dosage form is an amount bioequivalent to 0.5 mg naltrexone or more.

16. The oral dosage form of claim 5 wherein the amount of antagonist released after 1 hour from said intact dosage form is an amount bioequivalent to 0.125 mg naltrexone or less.

17. The oral dosage form of claim 6 wherein the amount of antagonist released after 1 hour from said tampered dosage form is 0.5 mg naltrexone or more.

18. The oral dosage form of claim 6 wherein the amount of antagonist released after 1 hour from said intact dosage form is 0.125 mg naltrexone or less.

19. The oral dosage form of claim 1, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, pharmaceutically acceptable salts thereof and mixtures thereof.

20. The oral dosage form of claim 19, wherein the opioid agonist is selected from the group consisting of oxycodone, hydrocodone and pharmaceutically acceptable salts thereof.

21. The oral dosage form of claim 1, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

22. The oral dosage form of claim 21, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, pharmaceutically acceptable salts thereof and mixtures thereof.

23. The oral dosage form of claim 22, wherein the opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

24. The oral dosage form of claim 2, wherein the material comprises a cellulose polymer or an acrylic polymer that is insoluble in the gastrointestinal tract and impermeable to the opioid antagonist contained within the coating.

25. The oral dosage form of claim 24, wherein the cellulose polymer is selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, and mixtures thereof.

26. The oral dosage form of claim 24, wherein the acrylic polymer is selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

27. The oral dosage form of claim 1, wherein the dosage form provides sustained-release of the opioid agonist.

28. The oral dosage form of claim 27, wherein the dosage form is a sustained-release tablet or a sustained-release capsule.

29. The oral dosage form of claim 2 wherein said multiparticulates are in the form of inert beads coated with said antagonist and overcoated with said material.

30. The oral dosage form of claim 2 wherein said multiparticulates are in the form of a granulation comprising said antagonist and said material.

31. The oral dosage form of claim 2 wherein said multiparticulates are dispersed in a matrix comprising said opioid agonist.

32. The oral dosage form of claim 2 wherein said multiparticulates are contained in a capsule with said opioid agonist.

33. The oral dosage form of claim 3 wherein said matrix is in the form of pellets.

34. The oral dosage form of claim 33 wherein said pellets are dispersed in a matrix comprising said opioid agonist.

35. The oral dosage form of claim 33 wherein said pellets are contained in a capsule with said opioid agonist.

36. The oral dosage form of claim 1 wherein said tampering is by crushing.

37. The oral dosage form of claim 27 wherein said tampering is in a manner as to obtain an immediate release of said agonist.

38. The oral dosage form of claim 1 wherein said tampering is to make the agonist available for inappropriate use.

39. The oral dosage form of claim 1 wherein said antagonist does not significantly affect analgesia provided by the agonist.

40. A method of decreasing the abuse of an opioid agonist in an oral dosage form, comprising incorporating said opioid agonist into a dosage form of claim 1.

41. A dosage form comprising:

(a) an opioid agonist; and

(b) naltrexone in a substantially non-releasable form; wherein the agonist and naltrexone are at least partially interdispersed.

42. The dosage form of claim 41 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, salts thereof, or mixtures thereof.

43. The dosage form of claim 42 wherein the opioid agonist is oxycodone hydrochloride.

44. The dosage form of claim 42 wherein the opioid agonist is hydrocodone bitartrate.

45. The dosage form of claim 42 wherein the opioid agonist is hydromorphone hydrochloride.

46. The dosage form of claim 41 wherein at least part of the naltrexone is in a matrix.

47. The dosage form of claim 41 wherein at least part of the naltrexone is in a coated bead.

48. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 15% by weight of the naltrexone *in vivo* after 36 hours.

49. The dosage form of claim 48 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 8% by weight of the naltrexone *in vivo* after 36 hours.

50. The dosage form of claim 49 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1% by weight of the naltrexone *in vivo* after 36 hours.

51. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 3% by weight of the naltrexone *in vivo* after 1 hour.

52. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1.0% by weight of the naltrexone *in vivo* after 1 hour.

53. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 0.5% by weight of the naltrexone *in vivo* after 1 hour.

54. A dosage form comprising:

(a) an opioid agonist; and

(b) an orally-bioavailable opioid antagonist in a substantially non-releasable form;

55. The dosage form of claim 54 wherein the agonist and antagonist are at least partially interdispersed.

56. The dosage form of claim 54 wherein the orally-bioavailable opioid antagonist is naltrexone, or a salt thereof.

57. The dosage form of claim 54 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, or salts thereof or mixtures thereof.

58. The dosage form of claim 54 wherein at least part of the antagonist is in a matrix.

59. The dosage form of claim 54 wherein at least part of the antagonist is in a coated bead.

60. A method of preparing an oral dosage form comprising pretreating an opioid antagonist to render it substantially non-releasable; and combining the pretreated antagonist with a releasable form of an opioid agonist.

61. A method of treating pain comprising administering to a human patient a dosage form of claim 1.

62. A composition comprising an inert core, a first layer and a second layer, the first layer being between the core and the second layer, the first layer consisting essentially of an opioid antagonist and the second layer comprising a hydrophobic material.

63. A composition comprising an inert core, a first layer and a second layer, the first layer being between the core and the second layer, the first layer comprising naltrexone, nalmefene, or pharmaceutically acceptable salts thereof and the second layer comprising a hydrophobic material.

64. The composition of claims 62 or 63 wherein the composition comprises from about 12% to about 15% hydrophobic material by weight of the composition.

65. A composition comprising an inert core, a first layer, a second layer and a third layer, the first layer being between the core and the second layer, the second layer being between the first layer and the third layer, the first layer comprising an opioid antagonist, the second layer comprising a first hydrophobic material and the third layer comprising a second hydrophobic material.

66. A composition comprising an inert core, a first layer, a second layer and a third layer, the first layer being between the core and the second layer, the second layer being between the first layer and the third layer, the first layer comprising naltrexone or a pharmaceutically acceptable salt thereof, the second layer comprising a first hydrophobic material and the third layer comprising a second hydrophobic material.

67. The composition of claim 66, wherein the first hydrophobic material and second hydrophobic material are different.

68. The composition of claim 66, wherein the composition comprises about 22% hydrophobic material by weight of the composition.

69. A composition comprising an opioid antagonist and a hydrophobic material, with the proviso that the composition does not comprise an opioid agonist.

70. The composition of claim 69 in the form of a matrix.

71. A composition consisting essentially of an opioid antagonist and a hydrophobic material.

72. The composition of claim 71 in the form of a matrix.

73. A composition comprising an opioid antagonist and from about 93% to about 98% of a hydrophobic material by weight of the composition.

74. The composition of claim 73 in the form of a matrix.

75. An oral dosage form comprising an opioid agonist and the composition of claim 63.

76. The oral dosage form of claim 75, wherein the opioid agonist is alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone,

hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, novlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, a pharmaceutically acceptable salt thereof or mixtures thereof.

77. The oral dosage form of claim 76, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof.

78. The oral dosage form of claim 76, wherein the opioid agonist is hydrocodone or a pharmaceutically acceptable salt thereof.

79. An oral dosage form comprising an opioid agonist and the composition of claim 63 comprising from about 14% to about 22% hydrophobic material by weight of the oral dosage form.

80. The oral dosage form of claim 79, wherein the opioid agonist is alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, novlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine,

piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, a pharmaceutically acceptable salt thereof or mixtures thereof.

81. The oral dosage form of claim 80, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof.

82. The oral dosage form of claim 80, wherein the opioid agonist is hydrocodone or a pharmaceutically acceptable salt thereof.

83. An oral dosage form comprising an opioid agonist and the composition of claim 68 comprising from about 91% to about 95% hydrophobic material by weight of the oral dosage form.

84. The oral dosage form of claim 83, wherein the opioid agonist is alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, novlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, a pharmaceutically acceptable salt thereof or mixtures thereof.

85. The oral dosage form of claim 84, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof.

86. The oral dosage form of claim 84, wherein the opioid agonist is hydrocodone or a pharmaceutically acceptable salt thereof.

87. The oral dosage form of claim 75, wherein the hydrophobic material is a biodegradable polymer, a cellulose polymer, an acrylic polymer or mixtures thereof.

88. The oral dosage form of claim 79, wherein the hydrophobic material is a biodegradable polymer, a cellulose polymer, an acrylic polymer or mixtures thereof.

89. The oral dosage form of claim 83, wherein the hydrophobic material is a biodegradable polymer, a cellulose polymer, an acrylic polymer or mixtures thereof.

90. The oral dosage form of claim 75 wherein the opioid antagonist is naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, a pharmaceutically acceptable salt or a mixture thereof.

91. The oral dosage form of claim 79, wherein the opioid antagonist is naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, a pharmaceutically acceptable salt or a mixture thereof.

92. The oral dosage form of claim 83, wherein the opioid antagonist is naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, a pharmaceutically acceptable salt or a mixture thereof.

93. A method for treating pain, comprising administering to a human patient in need thereof an effective amount of the oral dosage form of claim 75.

94. A method for treating pain, comprising administering to a human patient in need thereof an effective amount of the oral dosage form of claim 79.

95. A method for treating pain, comprising administering to a human patient in need

thereof an effective amount of the oral dosage form of claim 83.

96. A composition comprising:

(a) an opioid antagonist and

(b) means for sequestering the opioid antagonoist when the composition is orally administered.

97. The composition of claim 96, wherein the means for sequestering comprises a layer comprising a hydrophobic material.

98. The composition of claim 96, wherein the means for sequestering comprises from about 93% to about 98% of a hydrophobic material by weight of the composition.

99. The composition of claim 96, wherein the opioid antagonist is naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, a pharmaceutically acceptable salt or a mixture thereof.

100. An oral dosage form comprising:

(a) an opioid agonist;

(b) an opioid antagonist; and

(c) means for sequestering the opioid antagonoist when the oral dosage form is orally administered.

101. The oral dosage form of claim 100, wherein the means for sequestering comprises a layer comprising a hydrophobic material.

102. The composition of claim 100 wherein the means for sequestering comprises from about 93% to about 98% of a hydrophobic material by weight of the composition.

103. The oral dosage form of claim 100, wherein the opioid antagonist is naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, a pharmaceutically acceptable salt or a mixture thereof.

104. The oral dosage form of claim 100, wherein the opioid agonist is alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, novlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, a pharmaceutically acceptable salt thereof or mixtures thereof.

105. A method for treating or preventing pain, comprising administering to a human patient in need thereof an effective amount of the oral dosage form of claim 100.